

## BITS :: Call for Abstracts 2024 - Oral communication

<i>Type</i>	Oral communication
<i>Session</i>	Systems Biology
<i>Title</i>	Integrated metagenome- and metatranscriptome-scale metabolic modelling for uncultured microbial systems
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### *Motivation*

Genome-scale models of metabolism (GEMs) are effective tools for exploring the behaviour of microbial ecosystems and are increasingly used for this purpose. A great strength of GEMs is that they can guide the analysis and contextualisation of omics data. In particular, model integration of transcriptomics data is largely used to reproduce flux redirecting in individual microbes and simple artificial co-cultures in response to varying conditions. In contrast, current modelling approaches for more complex microbial systems are limited to considering the functional potential encoded in microbial genomes, which can often be scarcely indicative of real functional activity. Current multi-omics modelling approaches are thus inapplicable to the vast majority of microorganisms that live in large consortia and cannot be easily isolated.

### *Methods*

Here, we present an approach, named CoCo, that extends condition-specific metabolic modelling to microbes by metatranscriptomics data incorporation in models at microbiome level. CoCo explicitly accounts for heterogeneous activity in different community members, which contributes to modulating flux levels along with microbial abundance (Figure 1). The approach is used as a core step of a culture-independent pipeline for modelling microbial activity and metabolite exchanges based on the reconstruction of metagenome-assembled genomes (MAGs) and associated genome-centric metatranscriptomes (GCMs).

### *Results*

We validated CoCo and the full pipeline by targeting two widely studied ecosystems: anaerobic digestion consortia and human gut microbiota. In the first case study, the system was composed of three continuous bioreactors fed on basal anaerobic medium with acetate as the sole carbon source, which were perturbed with exogenous hydrogen injection. A total of 69 MAGs and associated GCMs were reconstructed by using a hybrid short- and long-read shotgun sequencing analysis, collectively comprising communities of 13 up to 17 members depending on the sample. Flux balance simulations showed that metatranscriptomic data integration enables a more accurate estimation of microbial growth rates and production of the main metabolites, including methane and carbon dioxide (Figure 2). Moreover, we characterised the differences in microbial activity between the feeding regimes and identified critical amino acid dependencies in archaeal species.

In the second case study, we focussed on a cohort of subjects suffering from Crohn's disease and healthy controls. In this case, we used an alternative workflow exploiting a collection of reference genomes and MAGs, reconstructing the associated GCMs and modelling microbial communities composed of 22 up to 91 taxa. Also here, the prediction of microbial growth rates improved with the use of CoCo, even with approximate information on subject dietary intake. Moreover, a positive correlation between community-level short-chain fatty acid export and metabolomics abundances was found, indicating that meaningful microbial activity was correctly captured by CoCo GEMs. Concomitantly, while functional potential and activity highly varied across subjects, CoCo GEMs suggest a decrease in the cross-feeding of these metabolites in Crohn's disease individuals both in terms of number of engaging microbes and total flux.

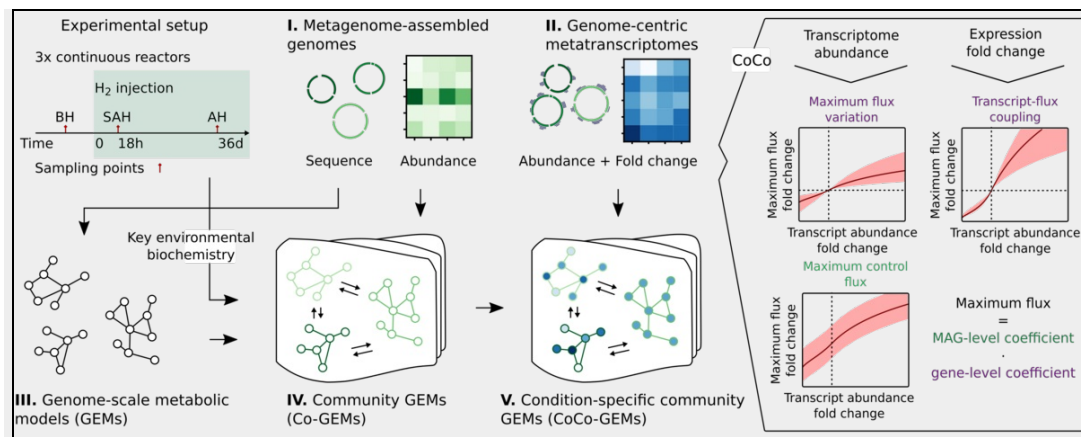
Our work takes a step forward into integrating multi-omics data and knowledge on a metagenome scale in real microbial ecosystems, providing two alternative use cases where CoCo can be applied: with de novo MAG reconstruction or, alternatively, exploiting existing genomes. Altogether, the results contribute to the systematic investigation of microbial ecosystems by bridging metagenomics and genome-scale modelling. Our approach can be applied to complex microbiomes, starting to disclose multi-omic metagenome-scale modelling and providing a new tool for investigating natural ecosystems.

### *Info*

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*filename* CoCo workflow.png

### *Figure*



Availability -

**Dissemination Material**

Social

Summary

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